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QUALITY BY DESIGN: A PRE-REQUISITE FOR PHARMACEUTICAL DEVELOPMENT

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ABSTRACT: Quality by Design (QbD) is an essential part of modern pharmaceutical development. QbD is a requisite for the design and development process for the pharmaceutical industry. QbD assists and encourages both the industries and FDA to inculcate a proactive, scientific and risk-based approach in the process and product development. It is based on a concept of building quality right from the start of the process rather than the final quality test of the finished product. An effective QbD approach provides insights and essential upstream throughout the development process which ultimately ends up offering a successful plan that reduces batch failures and recalls. It is also known as a structured lifecycle of product development and management. This review aims to present an overview of QbD implementation, its tools, elements, and methodologies, the involved ICH Guidelines, and the application in the current pharmaceutical sector. Under QbD, it is important to define the desired product performance profile *i.e.*, Quality Target Product Profile (QTPP) and analyze, Critical Quality Attributes (CQA), Critical Process Parameter (CPP), Critical Material Attributes (CMA), and Control Strategies. It also assists in reducing down the total product development cost and time. Eventually, it has now turned out to be a quality standard for designing and launching new products.

INTRODUCTION: The definition of quality differs from person to person, and hence an optimum description of Quality through Quality by Design (QbD) is a prerequisite for understanding the concept of pharmaceutical product development. Generally, quality ensures scientifically derived product and process performance objectives while exhibiting minimal batch-to-batch variations.

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As per the ICH Q8 guideline, Quality represents the suitability of either a therapeutically active substance or the entire therapeutic product for its intentional use. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER), extends a parallel yet exacting definition of quality as a drug product that is free from contamination and delivers reproducibly the promised therapeutic benefit indicated in the label to the consumer [1].

Earlier, the relationship of product attributes to product quality was not very well nuanced, and thus FDA has laid down quality specifications based on the observed exhibiting property, constraints of sponsors to fix down a manufacturing process and clinical test batches. The idea of experimental design started back in

1920. The prestigious work of Sir Ronald Fisher provided a base for statistical envisage in science and industrial applications. His work was further expanded by Quality experts like Walter A. Shewhart, William E. Deming, and Joseph M. Juran, they promoted the need for a process-centered view to inbuilt quality in the products. Juran coined the term "Quality by Design" to emphasize the importance of planning quality into products and processes involving five steps, *i.e* identifying the customer, determining his needs, translating these requirements as attributes of that product, developing the most suitable process and later carry it to operations [2]. Quality by Design (QbD) is defined as a scientific, systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, supported by sound science and quality risk management [3].

The backbone of QbD is "planning of quality," and therefore, the rationale for its implementation is Juran's trilogy of quality planning, quality control, and quality improvement [4]. The elements of QbD include: (i) the definition of a quality target product profile (QTPP) (ii) the identification of the Critical Quality Attributes (CQAs) of the drug product; (iii) the identification of Critical Material Attributes (CMAs) and (iii) the identification of Critical Process Parameters (CPPs) linked to CQAs through RA; (iv) definition of a Design Space (DS) and (v) identification of a Control Strategy that features specifications for the drug substance (s), excipient (s) and drug product together with controls for every step of the manufacturing process allowing a continual improvement.

The tools of QbD comprise (i) Risk assessment, (ii) Design Space, (iii) Process analytical technology (PAT), (iv) Design of Experiments (DOE), (v) Ishikawa Diagram. The aforementioned elements and tools are pillars of quality by design concept, each one of them is associated with the other and has a distinguishable, systematic and pivotal role in experimental practices. The first drug product developed by implementing QbD, approved in 2006 was Merck's Januvia for the treatment of diabetes, in the USA. However, this product was an outcome of a Qbd tool, *i.e* Design space. Later in the year 2013, FDA approved the first therapeutic product implementing QbD with a desirable DS-the Biologic License Application for Gazyva (obinutuzumab) by Genentech [5]. In recent times, pharmaceutical QbD has advanced with the advancement of ICH Guidelines involving ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH10 (Pharmaceutical Quality System). This review intends to provide a brief overview of Pharmaceutical QbD, its elements, tools, objectives and applications to lessen the gap between the conventional and 21st-century drug development process.

Elements of QBD:

Quality Target Product Profile (QTPP): Target Product Profile (TPP) is the base for Quality Target Product Profile (QTPP). TPP identifies the clinically relevant quality target including the performance criteria such as efficacy, stability and tolerability. TPP represents the requirements of the customer that must be supplied by the marketed preparations. It also lays the basis of design for product development, *i.e* it sets the predefined objectives of the product development cycle. According to ICH Q8 R(2), QTPP is defined as, a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product [4]. It gives the information of the drug at a particular time in the development step.

The first step includes the outlining of the quality target product profile (QTPP) followed by identifying the various critical quality attributes (CQA) that should be present in the product. Factors that define the product are included in the QTPP and these factors include dosage form, dosage strength, delivery system, route of administration and the intended use of the product, container closure system, drug release and factors affecting pharmacokinetic parameters and quality criteria such as sterility, purity and stability [6, 7]. QTPP acts as a surrogate for facets of clinical safety and efficacy for an optimized design of formulation and manufacturing process.

Critical Quality Attributes (CQAs): ICH Q8(R1) defines CQA as the physical, chemical, biological, or microbiological properties that should be in an appropriate limit, range, or distribution to ensure

The specified desired product quality [8]. Some describe CQA as the elements of CQA (dissolution studies) while some describe it as a mechanistic factor (particle size and hardness) and similarly, some assume it as the attribute of the final product and a few assume it attributes of intermediates or raw material. CQA is analogous with the drug substance, intermediates, final product, and excipient [9]. The drug product includes purity of the drug, assay, release (dissolution, disintegration and aerodynamic properties), stability (degradation level),, and sterility.

And related to raw material, excipients, and intermediates, it includes particle size, bulk density, granule size, and residual solvent content *e.g.* Studies show that the raw material attributes can cause the batch to batch variation resulting in a less robust process, in such case the particle size of the drug product and excipients is regarded as CQAs. Quality Target Product Profiles (QTPP) are metrics of patient and clinical outcomes. Critical Quality Attributes (CQA) are the quality metrics for drug products/substances. Both QTPP and CQA provide a framework for the designing of the resulting product and its understanding, which is achieved by characterizing the solubility, stability, compatibility, etc. of a substance through experiments on different formulations [10].

Critical Process Parameters (CPPs): Critical Process Parameters are the variables that have an impact on the Critical Quality Attributes. The Process Parameters (PPs) involve variables like temperature, humidity, method of granulation, compression force etc. [11]. These variables can be an assigned value and act as control levels or operating limits. CPP includes those variables that would have some serious impact on the quality attributes eg, temperature, pH, cooling rate, rotation speed, etc [2]. Usually, not all the PPs have an impact on the CQAs, but some important ones do. Therefore, it becomes extremely important to prioritize CPPs over other process parameters and should be controlled rigorously. CPPs must be monitored to enable early and accurate detection of deviations outside acceptable limits that will impact product quality.

Critical Material Attributes (CMAs): Another term often used when determining CPPs and their impact on CQAs is Critical Material Attributes (CMA). It is associated with input materials and their chemical, physical, biological, or microbiological properties [1]. The complexity of manufacturing any nonconventional dosage form can be significantly reduced by QbD. The manufacturing difficulty is due to multi-step processes and limited understanding of materials impacts and associated interaction. QbB is beneficial because it provides a complete understanding and a systemic path to discover the relevant inputs and the linked quantitative relationships. CMA are often excipient CMA, raw material CMA, drug substance CMA, starting material CMA.

It includes porosity, specific volume, impurity profile, particle size distribution, moisture level, etc., and maybe quantified. Although dissolution is taken into account as CQA, the set of critical material attributes independent of each other can provide a specific goal for evaluating a manufacturing process. As an example, a dissolution test may depend upon particle size and hardness [8]. Particle size and hardness are critical material attributes and may be directly linked with raw material and manufacturing process parameters.

Independent CMAs are the best mechanistic link of product quality to critical process parameters within the manufacturing process. In the scope of QbD, pharmaceutical quality is ensured by a comprehensive understanding and control of Formulation Attributes (FA) and PPs. For an effective QbD implementation, the CPPs and CQAs can vary reasonably within the DS provided they do not have any impact on the CQAs because ultimately the standard quality of the final product should meet the QTPPs [5].

Control Strategy: According to ICH Q10, Control Strategy is a planned set of controls acquired from current product and process understanding that resolute the operation performance and also the merchandise quality [12]. The controls include various parameters likewise as attributes associated with the drug and its final product material and components, facility and conditions for operating the types of equipment, IPQC, finished product specifications, associated methods and frequency of

monitoring and control. The ISPE PQLI Control Strategy Team has proposed a Control Strategy Model, facilitating the understanding of a cross-functional communication tool.

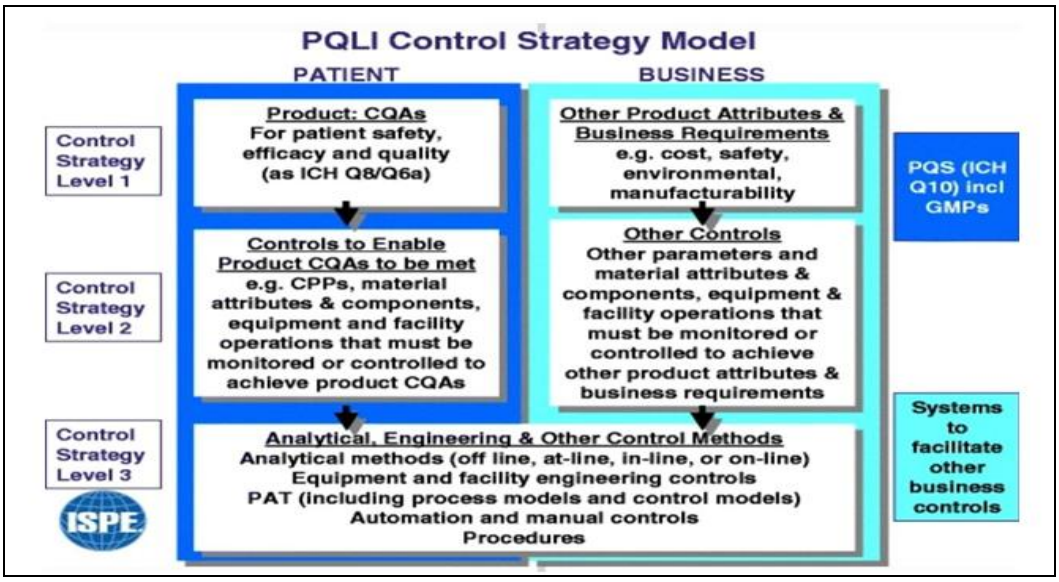

FIG. 1: THE PQLI CONTROL STRATEGY MODEL

The model **Fig. 1** represents a starting point which is the determination of CQAs based on the QTPP, and the endpoint is the distribution of the end product. It is a 3 level model depicting the link between the controls and CQAs to meet the standard quality throughout the manufacturing process.

At control strategy level 1 the CQAs are identified based on patient's safety, efficacy, and quality derived from the QTPP using knowledge from prior studies and experimentations along with clinical experiences and product-process under-standing. Control strategy level 2 includes the CQAs and other requirements determined to level 1 of the same.

This distinguishes the attributes that need to be monitored and controlled, such as attributes of starting material, reagents, solvents, process aids, operating procedures and conditions, equipment, and facilities. Finally, at control strategy level 3, analytical instruments and methods are considered. This includes the measurement technologies for material attributes or equipment parameters (off-line, at-line, in-line and on-line), univariate, multivariate and control process models, procedural and engineering controls of the plant e.g., Automation systems, closed control loops, normal operating ranges, and alarms [13]. It should also brief about what a process model should do and how it will be operated and maintained.

Tools:

Risk Assessments: Risk Assessments are performed at an early stage and are repeated several times at different stages to obtain more knowledge. Quality risk management (QRM) also verifies any changes in the product design. Further, comprehend ding it and managing it rightly to ensure patient safety [14]. The key objective of risk assessments is to which material attributes and process parameters affect the CQAs as well as to understand and predict the source of variability in the manufacturing process that can be implemented to ensure that the CQAs are within the desired range. QRM ensures a high-quality product, identifying and controlling potential quality risks during development and manufacturing, using a realistic evaluation of the true level of risks that can occur [15].

One of the prime activities of QRM is the risk assessment, where the initial list of potential causes of risk that can affect CQAs may be reduced by prioritizing only the most significant risks. Thus, these risks can be controlled through the product development process and its life cycle [16]. One of the important steps in QbD is to establish the Failure Mode and Effects Analysis (FMEA) form containing rectifying and preventive actions to mitigate all the critical potential failures and risks to avoid defective products reach the customer [16, 17].

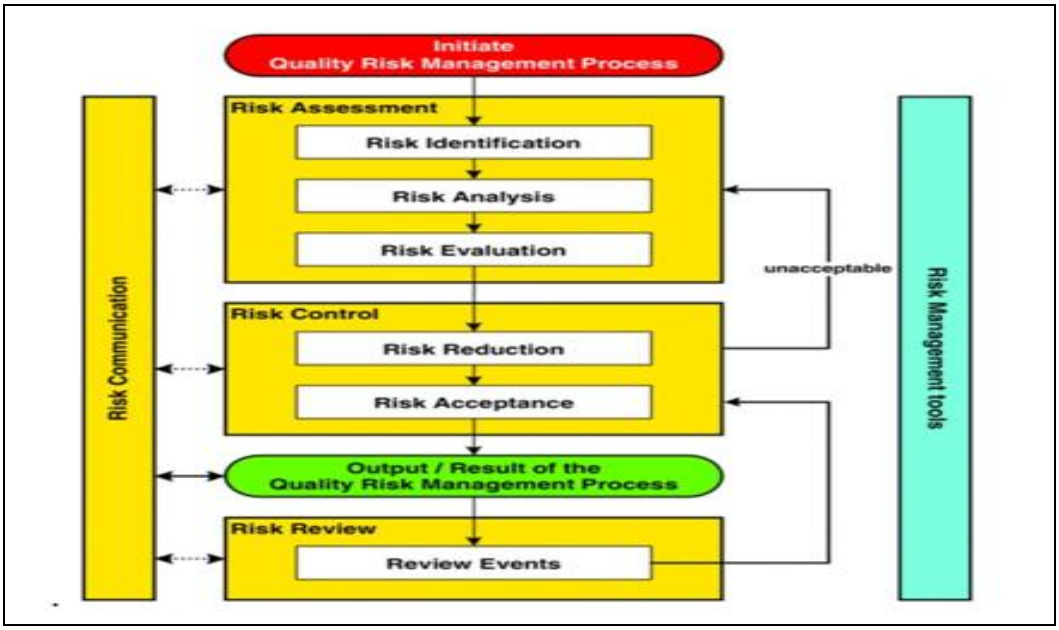

FIG. 2: OVERVIEW OF A TYPICAL QUALITY RISK MANAGEMENT PROCESS

Ishikawa Diagram: Ishikawa Diagram is also known as Fishbone Diagram and Cause-and-Effect Diagram **Fig. 3**. A fishbone diagram is another tool to highlight and display the potential causes of a problem in a well-organized pattern [18]. The cause-and-effect diagram along with organizing the function, also helps in inter-relating the effect of a particular cause on the system based on the theories and knowledge gained from the previous studies and reports. Development of a cause-and-effect model employs the concept of 5 M's *i.e.*, man, materials, methods, mother nature, and machinery, and the 4 P's *i.e*, people, procedures, policies [19].

Ishikawa diagram possesses the following characteristics: (1) Headbox of the diagram focuses on the actual problem or outcome to be improved. (2) The backbone of the "fish" is a long spine with an arrow pointing toward the head. The arrow direction should mimic the items; further intersecting along the spine might be the reason for the main problem. (3) The large bones attached to the spine represent the primary areas contributing to the problem. (4) Further, the smaller bones describe the more detailed causes of the quality problem and are related to the bone they are attached to, reflecting the major cause.

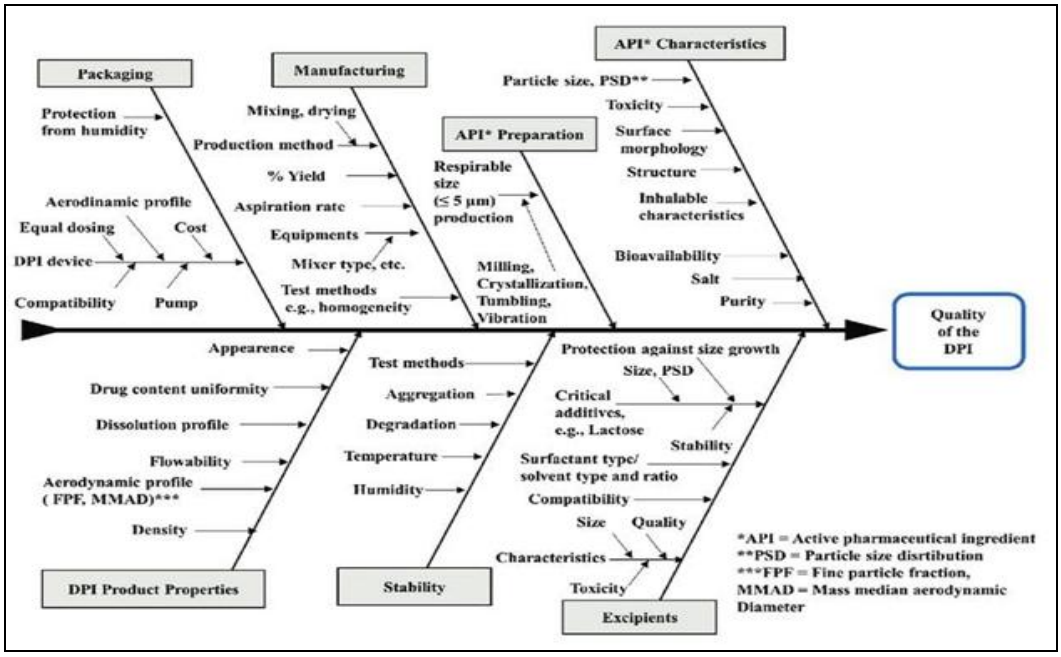

FIG. 3: GENERAL ISHIKAWA DIAGRAM FOR DPI FORMULATION

This orderly arranged pattern indicates a cause-and-effect model for the knowledge and understanding of the factors the impact quality from the deepest causes associated with a specified problem [20]. This diagram helps in the quick stimulation of a process as all the problem causative parameters are looked upon, discussed, and improved.

Design of Experiments (DOE): DoE is the Active Pharmaceutical Ingredient in the statistical toolbox of QbD. DoE is favored by ICH Q8 and used along with the multivariate data analysis (MVDA) method. A process is a value-adding function, transforming the sequences of inputs into outputs, influenced by various factors, regarded as controlled and uncontrolled, the latter is regarded as noise, as they in a occur random pattern and altogether have minimal effect compared to the controlled ones. However, the concept of experimental design categorizes the process variables into the potential design and nuisance factors that are later discriminated as controllable, uncontrollable, or noise. The latter is corresponding to uncontrolled and unavoidable variation, expressed by the experimental error. The impact of the controlled factors on the quality characteristics of the final product varies according to a general Pareto principle, indicating that a relatively minor character of factors are responsible for the essential percentage of the effect a. k.a the 20:80 rule, stating 20% of the causes (factors) are responsible for 80% of the results (responses) 2. DoE is an approach wherein the controlled input factors of the process are systematically varied to establish their effect on the responses. The net effect is the connecting the CPPs (x1, x2, xi) to the CQAs through mathematical functions y ¼ f(x), as described in **Fig. 4.**

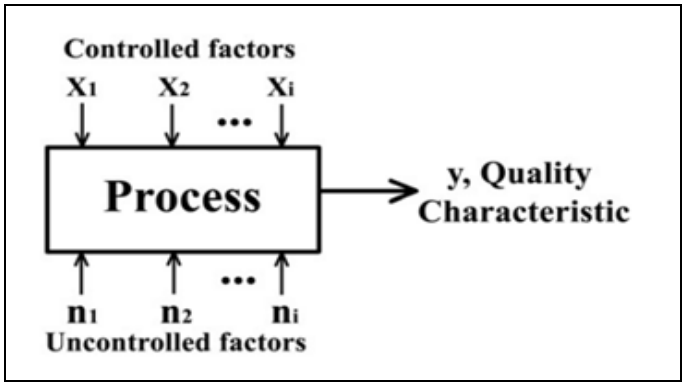

FIG. 4: SCHEMATIC PRESENTATION OF A PROCESS

It is favored by ICH Q8 and used along with the multivariate data analysis (MVDA) method. DoE is classified into screening design and optimized design. It establishes a cause and effect relationship between CPPs and CQAs and enables the optimization of CQAs by appropriate selection of CPP settings. The application of DoE involves maximum process knowledge with minimum resource use. It provides effective and most accurate information by identifying factor interactions and characterizing the significance of each factor 2. It also predicts process behavior within the design space.

Design Space (DS): The relationship between the CPPs and CQAs allows understanding of process behavior at different factor levels. A Design Space is a multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters, performed to assure product quality [21]. Product processes imparting quality, safety, and efficacy on a product are included in it. After the establishment of the design space, the next step is validation and regulatory filling. The regulatory filing will be approved if all the critical operating parameters are in an acceptable range. Working within or changes within the design space is not considered as change and will not require any supportive regulatory approvals [1].

Process Analytical Techniques (PAT): ICH Q8 suggests the use of Process Analytical Technique to ensure that the process remains within an established Design Space. Also, PAT is categorized under the control strategy. It is defined as "Tools and systems that utilize real-time and rapid measurements during the processing of evolving quality and performance attributes of an in-process material, providing information ensuring the optimal processing to develop the final product that consistently conforms to pre-determined quality and performance standards" [3].

According to works of literature PAT is a three-step process applied for designing and optimizing the drug formulations and manufacturing processes *i.e.*, design, analysis, and control [31]. In the first step, the impact of raw material attributes and PPs on the unit operations and final product are studied through experimentation, demonstrating the related quality attributes.

The knowledge obtained is then used to categorize the QTPP, CPP, and CQA, considered in developing an effective PAT-based control system [23]. The next step identifies the raw materials, PPs, chosen quality attribute, and a process measurement system, allowing real-time monitoring for all CQAs and CPPs, generally by direct or indirect analytical methods and the appropriate analytical tools. Lastly, adjustments are provided by control strategies to ensure control of all CQAs and built the understanding of relationships between the CQAs, CPPs, and QTPPs to decide the required actions in the case of deviation of the process performance from the original optimal path or quality from the desired attributes [1].

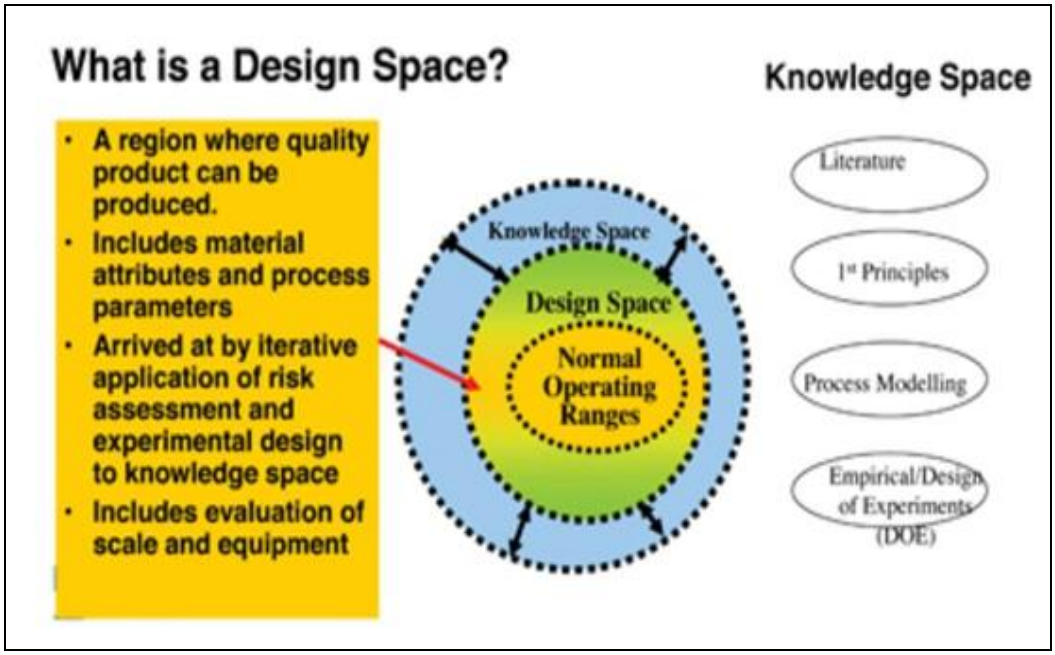

FIG. 5: REPRESENTATION OF A DESIGN SPACE

Objectives: The ideology behind Quality by Design science aims to furnish encouragement and support the development of quality right from the initiation of the product development process cycle by setting the essential pre-defined objectives to be fulfilled by both the product and the process.

The research and development phase) (R&D of a single new pharmaceutical product involves an average cost of $0.8 to $1.7 billion 24. Un fortunately, if the final product fails to meet the desired quality of the compendial standards and the regulatory bodies, it indicates an overnight loss of huge expenditure along with loss of a considerable number of years invested in the drug product development, right from the literature search stage to analyses of the final dosage form. Such incidents are extremely challenging for any pharmaceutical plant. In an attempt to bend down the upward rising graph of cost of development and regulatory barriers, FDA and ICH promote QbD in pharmaceuticals to achieve meaningful product quality as per the set standard specifications.

These standards are reasonable and are justified based on the clinical performance of the therapeutic dosage form. These standards setup as the predetermined objectives in cases of various FDA policies such as bead size in capsule labeled for sprinkle and tablet scoring [25].

In the R&D phase, the comprehension of formulation attributes and process parameters, the quantitative prophesy about their impact on CQAs of the process and the product are indeed the factors that pose to have a vital impact on the development of the product and process. Therefore, QbD is considered the key to achieving the quantitative understanding that would ultimately lead to the reduction of R&D times and costs. Besides R&D, QbD also delivers benefits to plant-scale routine manufacturing. Reports show that the cost of goods sold (COGS) is around 27-30% of the product's total cost for brand-name pharmaceuticals and roughly twice as much for generic drug manufacturers having substantially lower R&D, marketing and sales cost [26].

In regards to this context, QbD is crucial regardless of whether it is a branded or generic drug, it may reveal nuanced importance in reducing wastes and optimizing the profit margins of generics. The other objective of QbD is to quantitatively increase the process capabilities and deduct product variability to an appreciable level along with reducing the pharmaceutical defects by enhancing product and process design by understanding and applying control strategy. Implementation of such factors develops a product with a more efficient manufacturing process. This is because it helps to identify an efficient manufacturing process by analyzing different manufacturing variables at once, thus being time effective again. Eg. Analysing the effect of various formulation attributes on Drug release [1, 5]. Moreover, QbD enhances the root cause analysis and post-approval change management. Due to the root-cause examination, the levels of the factors affecting the desired quality can be easily noticed and being a systemic optimized approach; the levels can be altered to obtain a significant role. As a result, the professionals need not indulge in changing the entire framework but can directly look upon the exact factor responsible for the change and fix the level to an optimum value that will best suit the organization. In context with the post-approval changes, QbD tool act as a savior. Any change after the FDA Approval needs to be approved again. FDA approvals are one of the long-tedious processes but are the crown over any pharmaceutical industry. When an association employs QbD in the product development cycle, it is benefited from a lesser time duration for development as well as the approval process. Any change in the experimentation within the design space is not considered as a major change and thus does not requires any application for post-approval changes. US-FDA always welcomes risk assessment-based approaches, and QbD is a risk assessment approach [5].

Implementation of Qbd for Pharmaceutical Product Development: QbD simplifies the product development process in a well-organized pattern. This pattern is helpful in terms of flexible regulatory approvals and establishing a highly effective development procedure that results in time-saving, high returns on investment, and fewer recalls. Additional benefits include innovative processes with fewer batch failures, continual improvement, better control, automation, and transfer.

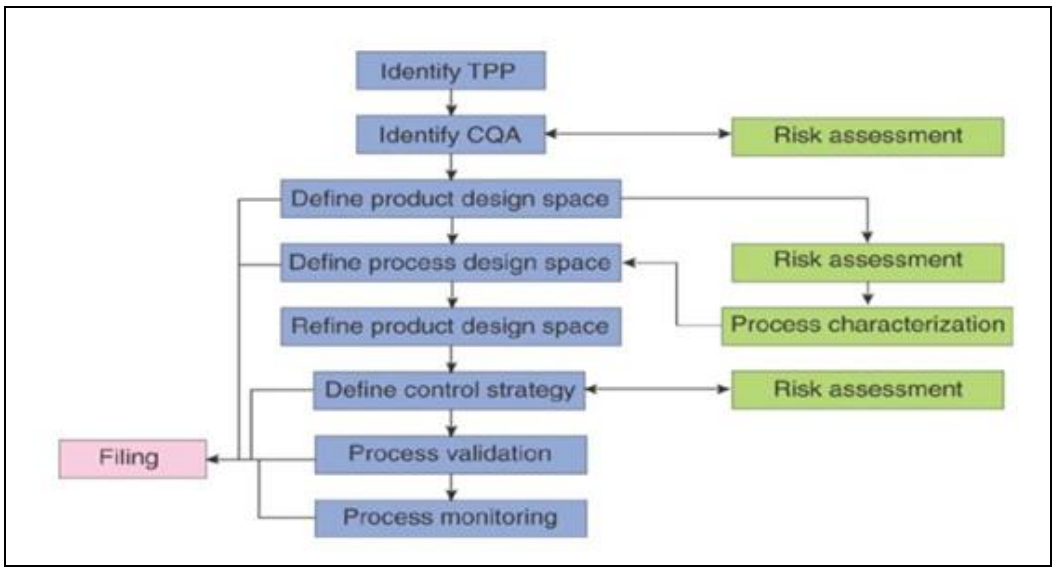

FIG. 6: KEY STEPS INVOLVED IN IMPLEMENTATION OF QBD FOR A PHARMACEUTICAL PRODUCT DEVELOPMENT

Identification of TPPs and QTTPs: This includes the dosage form, ROA, identity and strength, release profile and assay, pharmacokinetic parameters by the dosage form, purity, stability, label indications as per the intended market [27].

Identifying the CQAs: This step involves the risk assessments based identification as per ICHQ9. The key elements to building a risk assessment involve the prior product knowledge, such as accumulated laboratory, nonclinical and clinical

experiences with a specific product-quality attribute, obtained from data of relevant product from relevant literature.

Designing Product and defining Product Design Space: It defines the specification for in-process, drug substance, and product attributes. The specifications are established on information that interconnects the attributes to safety and efficacy of the product, including the published literature, process capabilities w.r.t variability in the manufactured lots, DS, clinical and nonclinical studies with similar platform products (in terms of physical, chemical, biological properties [28].

Process Designing and defining Process Design Space: This outlines the commercial manufacturing process. It considers the factors for designing the process, including the materials transfer, facilities, types of equipment, and manufacturing variables [29]. The DS determinations employ methods like the First principle approach (combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering for model development and performance prediction), Statistical DoEs, Scale-up correlations, and combination of any method. The DoE involves 3 steps. The first step i for process s risk analysis performed to identify parameters characterization. The next step is the study design step wherein the obtained data helps to define the DS. In the last step, the importance of parameters as well as their role in establishing the DS is analyzed.

Defining Control Strategy: The control strategy in the QbD paradigm is established *via* risk assessment that takes into account the criticality of CQAs and process capability. This includes procedural controls, in-process controls, lot release testing, process monitoring, characterization testing, comparative and stability testing.

Process Validation: An enhanced understanding of the manufacturing process and process design space provides more flexible manufacturing during process validation [30]. This is because the process design space assures the quality of the product, and the provided limits should form the basis of validation acceptance criteria. Once the process design space is created, process validation becomes an exercise to demonstrate that the process will deliver a product of acceptable quality if operated within the design space and the pilot-scale system used to establish the design space accurately, model the performance of the manufacturing scale process.

Regulatory Filings: After the process design space is established and validated, regulatory filing is the next step. Approval is based on the acceptable ranges for all critical operating parameters defining the DS. Additionally, it would include the redefined product design space, description of CS, validation outcome and plan for process monitoring. In the QbD paradigm, the filing also includes protocols allowing the flexibility in the process chance concerning the pre-approved criteria that have been agreed upon the agreed upon between the applicant and agency (eg. comparability protocol or expand change protocol)

Process Monitoring, Life cycle Management, and Continual Improvement: The basis of a filed process design space is continual monitoring of CQAs after the approval, ensuring that the process is performed within the defined acceptable variability. As the manufacturing experience grows the ways for process improvement are identified. The operating spaces could be revised within the design space without the need for post-approval submission [31]. The backbone of continuous improvement is Pharmaceutical Quality System (PQS). PQS facilitates continual improvement and helps to: "Identify and implement appropriate product quality improvement, thereby increasing the ability to fulfill quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement [32]. The robustness of a quality system needs to be demonstrated for four elements namely, process performance/ product quality monitoring; preventative/ corrective actions, management changes and review of the management of the product and process quality.

Future of QBD: QbD is not an age-old concept. It belongs to the 21st century era parameters for quality development in pharmaceuticals. This concept has gained tremendous response thought the globe and it is already been followed in various industries and researches. This also has received acceptance by FDA after its innovation and in

today's scenario, any research or ongoing process with applying QbD is not considered up to the mark. QbD is extensively employed by various industries by using various software to develop new dosage forms. QbD is definitely here to stay as it is a risk-based approach and risk-based approaches are always welcomes by FDA Regulatory Authorities.

Although understanding the fundamental knowledge and technical tools for systematic innovative pharmaceutical manufacturing principles is possible today, still more appropriate work is required mainly to adjoining the pharmaceutical sciences and engineering tools that essentially create pharmaceutical engineering science. It is always as per the ICH guidelines and gives a guiding direction to invest expenditure and time in the right place to obtain the right quality that suits the patient requirements.

CONCLUSION: This work centers on delivering an outline of QbD and its attributes in the modern pharmaceutical product development process. QbD focuses on building quality into the product and processes, as well as continuous process improvement- reduction of variability. The foremost interesting benefit of QbD implementation is its cost-effectiveness.

By being cost-effective, it does not mean a fall of price from its peak value to value but it means utilizing the involved expenditure the minimum in a very right manner as QbD focuses in an optimal manner of building the required quality right from the initiation of the cycle instead of investing money on failures and recalls. Lastly, the essential attributes for producing high-tech quality pharmaceuticals are established, gaps are identified, the following step is the need for a joint effort of academia, industries, and regulatory agencies to begin the implementation of QbD principles in practice.

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